REMARKS

Claims 2, 3, and 20-22 are canceled herewith. Thus, pursuant to the entry of the instant amendment, claims 1, 4-10, 12-19, 24-37, and 39-51 are presently pending, with claims 6-10, 14-19, 24-37, and 39-51 withdrawn from consideration as directed to non-elected inventions (methods and compositions of Groups I and III-XXII). Accordingly, substantive examination is presently limited to method claims 1, 4-5, 12, and 13.

In an effort to expedite prosecution, independent claim 1 has been amended to incorporate the limitations of claim 22, now canceled. In addition, so as to assuage the Examiner's enablement and indefiniteness concerns, Applicants have attempted to clarify the character and construction of the blood plasma preparation set forth in part (b) of claim 1. As discussed in greater detail below, the criticality of the present invention lies in the removal of the pro-coagulatory-acting factors, isoagglutinins, lipoproteins and toxic lipids native to human blood plasma, with all other native components (e.g., plasma proteins, anti-coagulatory-acting factors and residual immunoglobulins) being virtually unchanged. By excluding those components of blood plasma that could evoke undesired reactions (such as, for example, the attachment of antibodies to antigens on the surface of endothelial cells, complement activation, and the initiation of the blood clotting cascade), Applicants are able to reduce the occurrence of post-implantation thrombosis and stenosis. In addition, though not wishing to be bound by theory, the observed improvement in endothelium preservation associated with the blood plasma preparation-containing perfusion solution of the present invention is most likely due to additional factors that are present in the blood plasma, including, for example:

(a) hormones and growth factors that are beneficial for the repair and maintenance of the endothelial tissues in the lumen of the vessels and the coating of endothelium-damaged vascular walls;

(b) transport proteins, such transferrin and ceruloplasmin, that are beneficial for substantial enzyme functions in the endothelium and signal transduction processes in endothelial

cells;

(c) antithrombogenic proteins, such as antithrombin III, protein C, and tissue-factor-inhibitor;

(d) a variety of further plasma proteins that are necessary to stabilize the important luminal endothelial surface layer, the so-called "glycocalyx", which has been intensively investigated in recent years and found to be an essential component of the endothelial barrier between the blood and deeper layers of the vessel wall; and

(e) serpins for the elimination and/or inactivation of thrombin and other mediator proteins of the inflammatory processes that would otherwise immediately activate the subendothelial pericytes, components now known to be important mediators of thrombosis, atherosclerosis and saphenous vein graft disease.

In support of point (e) above, Applicants wish to direct the Examiner's attention to their recent publication entitled "*Pericytes In The Macrovascular Intima: Possible Physiological And Pathogenetic Impact*" (Juchem, G et al., Am J Physiol Heart Circ Physiol (December 18, 2009), doi:10.1152/ajpheart.00343.2009, published online as an article in press) that describes for the first time the pathogenic potential of these newly detected cells. A complete copy of the Juchem et al. article is provided herewith as Appendix A.

Support for the claims as amended herewith is found in the specification as originally filed, for example at page 25, lines 7-8, wherein "unstable components" are defined as, for example, "lipoproteins and other toxic lipids". Thus, Applicants respectfully submit that no new matter has been added. However, Applicants reiterate that these amendments are presented solely for the purpose of expediting prosecution and should not be construed as Applicants' agreement with or acquiescence to the grounds of rejection previously set forth.

Turning to the outstanding Office Action of September 30, 2009:

Election/Restriction:

Applicants confirm their election of the invention of Group II but reiterate their traversal of the restriction requirement, particularly as applied to certain dependent claims. The Examiner admits at page 2 of the September 30th Office Action that "composition A may not be restricted from compositions A+B or from A+B+C, or from A+B+C+D as these form a tree of further limitations". However, this statement seems to be in conflict with the withdrawal of dependent claims 6-10, which merely further define the "physiological electrolyte solution" and "nutrient substrate" set forth in elected claim 1 as components (a) and (c), respectively. Likewise, withdrawn claims 14-19 merely set forth various supplemental components that may be added to the perfusion solution of claim 1 (i.e., growth factors, flavenoids, adenosine, cardioplegic concentrations, etc.) Applicants respectfully submit that these dependent claims comport to conventional practice, further defining the elected invention in terms of preferred formulations rather than setting forth independent and distinct embodiments thereof. Thus, Applicants respectfully petition for reconsideration and reentry of dependent claims 6-10 and 14-19.

In the event the Examiner maintains the outstanding restriction, either all or in part, Applicants reserve the right to present any non-elected claims in one or more divisional applications. Applicants further reserve the right of rejoinder in accordance with the provisions of 37 C.F.R. § 1.104. To that end, Applicants wish to remind the Examiner that upon the allowance of a generic claim, Applicants are entitled to consideration of claims to additional species that depend from or otherwise require all the limitations of an allowable generic claim. M.P.E.P. § 806.04(d).

Enablement Rejections:

Claims 1, 3-5, 12, 13 and 20-22 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. According to the Examiner, the claims contain subject matter that was not described in a way as to enable one skilled in the art to make and/or use the claimed invention. In particular, the Examiner asserts that the process for making the "homologous anti-coagulatory blood plasma preparation" component, set forth in claim 1(b), is not sufficiently disclosed in the specification. Applicants respectfully disagree.

At the outset, Applicants wish to point out that the cancellation of claims 3 and 20-22 renders the rejection thereof moot. As for the remaining claims, it is important to note that a specification is presumed to be in compliance with the enablement requirement of section 112, first paragraph. The burden is therefore on the Patent Office to establish a reasonable basis to question enablement. To that end, the test of enablement is whether one reasonably skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation. For an Examiner to sustain a rejection on the grounds of enablement, she must provide evidence that the claimed method could not be performed without such undue experimentation.

Many factors must be considered when determining whether the specification is enabled and whether any necessary experimentation is "undue". They include: the breadth of the claims; the nature of the invention; the state of the prior art; the level of ordinary skill in the art; the level of predictability in the art; the amount of direction provided by the inventor; the existence of working examples; and the quantity of experimentation needed to make or use the invention. In this case, Applicants respectfully submit that, given the specific direction in the claims, the high skill level of the average artisan, and the evolved state and reasonable predictability of the art of plasma processing, any experimentation necessary to replicate the disclosed invention falls well within ordinary skill, and is indeed routine.

In support of her challenge to enablement, the Examiner cites to the complexity of plasma, a blood derived liquid composed of at least 100 diverse proteins, and contrasts it with the "sparse guidance" and "lack of detail" provided in the disclosure spanning pages 27 and 28. However, Applicants respectfully take issue with the Examiner's characterization of the disclosure and wish to remind the Examiner that it is well accepted, and indeed preferable, for an applicant to omit descriptions of well-known techniques from a patent specification. Applicants respectfully submit that the present specification conforms to that preference and any gaps in the instant disclosure may be readily filled with conventional knowledge. In other words, the fact that the instant specification does not expressly recite the specific anion chromatography conditions, elution conditions, filtration solvents and/or variety of DEAE Sephadex or Aerosil is neither critical nor dispositive as information pertaining to these parameters is either known or readily available to those of skill in the art. Thus, Applicants respectfully submit that one skilled in the art, advised of Applicants' goal to remove the pro-coagulatory-acting factors, isoagglutinins and unstable components, such as lipoproteins and other toxic lipids from a blood plasma sample, while leaving intact the remaining plasma components, particularly the human plasma proteins, anti-coagulatory factors, and immunoglobulins, would readily be able to determine the suitable reactants and conditions and thereby make and use the "homologous anti-coagulatory blood plasma preparation" that is central to the compositions and methods of the instant invention.

Accordingly, Applicants respectfully submit that one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation and thus petition for reconsideration and withdrawal of the enablement rejection in view of the amendments and remarks presented herein.

Indefiniteness Rejections:

Claims 1, 3-5, 12, 13 and 20-22 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. According to the Examiner, it is unclear what is contemplated by the phrase "unstable components".

Again, Applicants wish to point out that the cancellation of claims 3 and 20-22 renders the rejection thereof moot. As for the remaining claims, while Applicants respectfully disagree with the Examiner's characterization of the phrase "unstable components" as indefinite, they have nevertheless, in an effort to expedite prosecution, have replaced the objectionable phrase with illustrative examples of such components, namely "lipoproteins and toxic lipids". Accordingly, Applicants respectfully submit that the claims as amended herewith meet the threshold requirements for clarity and precision set forth in 35 U.S.C. § 112, second paragraph. As such, Applicants respectfully request reconsideration and withdrawal of the outstanding rejections of claims 1, 4-5, 12, and 13 in view of the amendments and remarks herein.

Prior Art Rejections:

Claims 1, 3-5, 12, and 20-22 stand rejected under 35 U.S.C. § 102(b) as anticipated by or, in the alternative, under 35 U.S.C. § 103(a) as obvious over US 4,073,886 (Kehm et al) or US 3,998,946 (Condie et al.). Claim 13 stands rejected under 35 U.S.C. § 103(a) as being unpatentable over Kehm or Condie as applied to claims 1, 3-5, 12, 20-22 above, and further in view of Dichtelmuller et al.

According to the Examiner, Kehm and Condie disclose treated plasma preparations for use in organ perfusion that appear to be similar to that utilized in Applicants' Example 1 and therefore would be reasonably assumed to inherently contain the claimed physiological electrolytes and nutrients. As for the differences in claimed parameters (e.g., concentrations, temperature ranges, target organ type), the Examiner asserts that, absent a demonstration of

criticality, discovery of optimum or workable ranges does not constitute inventive subject matter. With regard to claim 13, the Examiner asserts that, in view of the teachings of Dichtelmuller, one of ordinary skill in the art would have been motivated to treat the Kehm or Condie preparations with beta-propiolactone and UV irradiation in order to inactivate viruses contained therein.

Applicants again wish to point out that the cancellation of claims 3 and 20-22 renders moot the rejection thereof. As for the remaining claims, Applicants respectfully dispute the Examiner's characterization of the prior art teachings and her conclusions of anticipation and obviousness. Nevertheless, in an effort to expedite prosecution, Applicants have herewith amended claim 1 to clarify the construction and character of the presently claimed perfusion solution, to further distinguish it from the kidney perfusates of the cited prior art. Accordingly, Applicants respectfully petition for reconsideration and withdrawal of the pending anticipation and obviousness rejection in view of these distinguishing amendments and the following remarks:

In order to anticipate, a single disclosure must set forth each and every element of a claim. In this case, neither Kehm nor Condie disclose or suggest the preparation of a homologous anti-coagulatory blood plasma preparation from blood plasma that retains the human plasma proteins, anti-coagulatory-acting factors and immunoglobulins of blood plasma but is free from the pro-coagulatory-acting factors, isoagglutinins, lipoproteins and toxic lipids native thereto, much less the combination thereof with a physiological electrolyte solution and nutrient substrate to yield an endothelium-protective perfusion solution useful in preserving the endothelium of a biological vessel, such as a blood vessel or lymphatic vessel.

While Condie indeed discloses a plasma preparation having utility as an organ perfusion fluid, more particularly a kidney preservation solution, he expressly requires the resulting preparation to maintain "plasma coagulation factor II at pretreatment levels". Accordingly, his blood plasma preparation cannot be fairly characterized as "anti-coagulatory" nor can it be described as being "free from the pro-coagulatory-acting factors" native to human plasma. He

also fails to disclose or suggest combining the disclosed "fibrinogen-free, plasminogen-plasmin-free" plasma derivative with a physiological electrolyte solution and a nutrient substrate to yield an endothelium-protective perfusion solution used to preserve biological vessels. As such Condie cannot anticipate the invention of the pending claims.

Kehm similarly fails to disclose each and every element of the pending claims. While his plasma preparation is indeed described as having utility as an organ perfusion fluid, he fails to teach the selective removal of only the noted components, while leaving the remaining native components intact. He likewise fails to disclose or suggest combining his protein-free, lipid-free plasma derivative with a physiological electrolyte solution and a nutrient substrate to yield an endothelium-protective perfusion solution used to preserve biological vessels. Thus Kehm cannot anticipate the invention of the pending claims.

As for obviousness, it is important to note that three basic criteria must be met to establish a *prima facie* case of obviousness. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. However, even a *prima facie* case of obviousness may be rebutted by so-called "indicia of non-obviousness", e.g., evidence of secondary considerations such as unexpected results, commercial success, long felt but unsolved needs, failure of others, etc. In particular, evidence that a claimed invention yields unexpectedly improved properties or properties not present in the prior art and/or evidence that the claimed invention possesses unexpected properties is generally sufficient to overcome a *prima facie* case of obviousness. See *In re Dillon*, 919 F.2d 688 at 692-93, 16 USPQ2d 1901 (Fed. Cir. 1990); *In re Albrecht*, 514 F.2d 1389, 1396, 185 USPQ 585, 590 (CCPA 1975).

In this case, the Examiner asserts that any differences between the prior art and the presently claimed invention are minor in character (not patentably distinguishing), and thus,

absent a demonstration of criticality, are presumed to be obvious. However, Applicants respectfully submit that the novel endothelium-protective perfusion solution of the instant invention – composed of at least (i) a physiological electrolyte solution, (ii) a nutrient substrate, and (iii) a homologous anti-coagulatory blood plasma preparation free from the pro-coagulatory-acting factors, isoagglutinins, lipoproteins and toxic lipids native to blood plasma but retaining all other human plasma components, including plasma proteins, anti-coagulatory-acting factors and immunoglobulins – offers numerous unexpected advantages in the context of preserving explanted blood vessels.

To that end, Applicants wish to direct the Examiner's attention to a post-filing publication of the present invention authored by Dominik R. Weiss et al., entitled "*Extensive Deendothelialization and Thrombogenicity in Routinely Prepared Vein Grafts for Coronary Bypass Operations: Facts and Remedy*" (Weiss et al., Int. J. Clin. Exp. Med. (2009), vol. 2, pp. 95-113), a copy of which is provided herewith as Appendix B. A primary objective of this study was to gain insight into saphaneous vein graft disease (SVGD) and find a practical approach to avoid it. To that end, the authors compared various conventional storage solutions, including saline, saline + 5% albumin, HTK-solutions, and heparinized autologous blood, to a novel plasma preparation available under the tradename "Biseko®"[1] that contains "all major plasma components apart from isoagglutinins and coagulation factors" and discovered that the plasma preparation was vastly superior to the others in terms of preserving the integrity and stability of the endothelium lining the vasculature, a necessary prerequisite to avoiding the downstream consequences of acute thrombosis, intimal hyperplasia and atherosclerosis.[2]

[1] Applicants respectfully submit that the blood plasma preparation utilized in Examples 9-11 of the instant disclosure is identical to Biseko® and direct the Examiner's attention to the legend of Figure 11.

[2] Erosion of the endothelium leads to exposure of the underlying pericyte-like cells of the subendothelium, cells believed to express exceptionally high concentrations of tissue factor (TF) and prothrombinase on their surface such that, when exposed to blood, they become an immediate focus for rapid coagulation process. See Weiss et al. at p. 96, column 2, paragraphs 2-3.

In particular, whereas "the widely used routine graft preservation protocols led, in the vast majority of cases, to extensive and indeed complete loss of the endothelium" (see Weiss @ p. 96, column 2, paragraph 3), the plasma preparation (PP) freed from isoagglutinins and coagulation factors preserved both the morphology and barrier function (relative impermeability) of cultivated endothelial layers, providing not only long term stability and survival to the endothelium, but, in certain conditions, actually promoting cell division and proliferation (see Weiss @ p. 99, column 2, as well as Figures 1 and 2 reproduced herein).

Deendothelialization and thrombogenicity

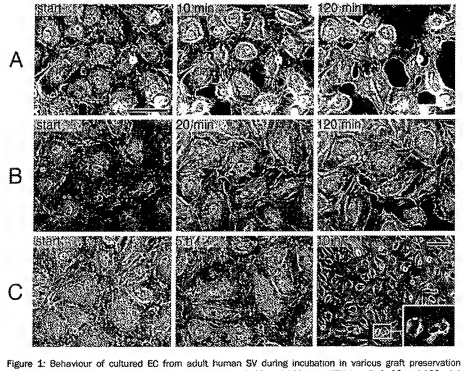

Figure 1: Behaviour of cultured EC from adult human SV during incubation in various graft preservation media. Incubation at room temperature in saline (row A: 0, 10 and 120 min), HTK (row B: 0, 20 and 120 min) or PP (row C: 0, 5 h and 10 h (37 °C, the inset shows dividing cells)). Common bar (80µm), with an exception in the last picture in row C (bar, 250µm).

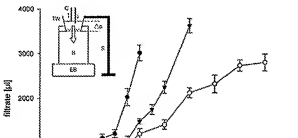

Figure 2: Permeability of cultured confluent endothelial layers exposed to graft preservation solutions. Inset: schematic drawing of apparatus, TW Transwell culture filled with preservation medium (PM), S stand to which TW is attached, C cannulae maintaining a constant pressure gradient Δp of 1.5cm H_2O via peristaltic pump and reservoir, B beaker filled with resp. solution, filtrate (boxed arrow) is monitored with an electronic balance EB. Time course of transendothelial filtrate of: saline (solid circles), HTK (solid triangles), saline + 5% albumin (open circles), PP (open triangles). Means ±SEM, n=8.

In addition, as noted in the above-referenced Juchem et al. publication (Juchem, G et al., Am J Physiol Heart Circ Physiol (December 18, 2009), doi:10.1152/ajpheart.00343.2009), a copy of which is provided herewith as Appendix A, the same plasma preparation (PP), freed from isoagglutinins and coagulation factors, also almost completely preserved the endothelium of coronary bypass vessels and thus prevented direct contact with the newly detected subendothelial pericytes in the macrovascular intima. As Applicants amply demonstrate in the Juchem publication, pericytes appear to be the primary focus of thrombogenetic and atherosclerotic processes in the vessel wall. The demonstrated preservation of the luminal endothelium in surgical bypass vessels therefore explains the fact that vessels preserved in PP are characterized by a very low thrombogenicity (see Weiss @ pp. 101-106) and a far better clinical prognosis.

Finally, the improved character of the plasma preparation of the instant invention has been further confirmed by Szolnoky et al. ("Biseko Colloidal Solution Diminishes The Vasoreactivity Of Human Isolated Radial Arteries", Euro J Cardiothorac Surg. (2009 Jul), vol. 36(1), pp. 143-7 – Abstract enclosed as Appendix C). The results of the Szolnoky study suggest

explant graft materials stored in Biseko®, as compared to albumin, crystalloid saline and Bretschneider solutions, were less sensitive to vasoconstriction and therefore less prone to graft failure.

Thus, Applicants respectfully submit that invention of the instant claims is not merely an obvious variation of a prior art process but rather a patentable invention having unexpectedly improved and scientifically and clinically already successfully demonstrated properties as compared to the prior art. Accordingly, Applicants respectfully request the Examiner reconsider and withdrawn her assertion of obviousness in view of the amendments and remarks herein.

CONCLUSION

The Office Action of September 30, 2009 set a three-month shortened statutory period for response. Further to the petition for one-month extension of time submitted herewith, response is due on or before **February 1, 2010** (January 30th being a Saturday). Accordingly, Applicants submit that this response is timely and no additional fees, apart from those included herewith, are required. However, in the event that further fees are required to enter the instant response and/or maintain the pendency of this application, the Commissioner is authorized to charge such fees to our Deposit Account No. **50-2101**.

If the Examiner has any questions or concerns regarding this communication, she is invited to contact the undersigned.

Respectfully submitted,

Date: **January 7, 2010**

By: **/chalin a. smith/**

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